

Improvement in solubility of poor water-soluble drugs by solid dispersion

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Abstract

This article is intended to combine recent literature on solid dispersion technology for solubility enhancement with special emphasis on mechanism responsible for the same by solid dispersion, various preparation methods, and evaluation parameters. Solubility behavior is the most challenging aspect for various new chemical entities as 60% of the new potential products possess solubility problems. This is the biggest reason for new drug molecules not reaching to the market or not reaches to full potential. There are various techniques to enhance the drug solubility such as particle size reduction, nanosuspension, use of surfactants, salt formation, solid dispersion, etc. From this article it may be concluded that solid dispersion is an important approach for improvement of bioavailability of poor water-soluble drugs.

Key words: Dissolution, electrospinning, eutectic mixture, hydrophobic drugs, lyophilization

INTRODUCTION

Solid dispersion (SD) has been widely used to improve the dissolution rate, solubility, and oral absorption of poor water-soluble drugs. SD refers to the group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug; the matrix can be either crystalline or amorphous.^[1] Solid dispersion was first introduced to overcome the low bioavailability of lipophilic drugs by forming eutectic mixture of drugs with water soluble carriers. Approximate 40% of new chemical entities (NCE) being synthesized by combinatorial screening programs possessing superior pharmacological activities are poorly soluble, which is a great obstacle in formulation development.^[2] Biopharmaceutical classification system (BCS) highlights the dissolution as rate limiting step for oral absorption of BCS class 2 and class 4 drugs. BCS class 2 and class 4 drugs have low solubility.

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Various techniques for enhancement of solubility of poor water-soluble drug

A number of methodologies can be adapted to improve solubilization of poor water-soluble drugs and further to improve its bioavailability.

Particle size reduction

The solubility of a drug is intrinsically related to the particle size. Reduction of particle size of a drug by various means such as jet mill, rotor stator colloidal mill, ball mill, etc. leads to increase in surface area with enhanced dissolution. But limitation of this process includes thermal and physical stress on drug product that leads to degradation. Other disadvantages include limited opportunity to control important characteristics of final product such as shape, size, morphology, surface properties, and electrostatic charges. Also, amorphous region are thermodynamically unstable and susceptible to recrystallization on in hot and humid condition.^[3,4]

Nanosuspension technology

Nanosuspension technology has been developed as a promising candidate for effective delivery of poor water-soluble drug. Nanosuspension is sub-micron colloidal dispersion of pure particles of drugs, which is stabilized by surfactants for either topical or oral use or parenteral or pulmonary administration. In nanosuspension, particle size is usually less than one micron ranging between 200 and 600 nm.^[5,6]

Media milling, high pressure homogenization in water, high pressure homogenization in non-aqueous media and combination of precipitation and high pressure homogenization are the various method of preparation of nanosuspension.^[7,8] Nanosuspension approaches have been employed for various drugs including tarazepide, atovaquone, amphotericin B, etc.

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Surfactant

The use of surfactant in enhancement of solubility of poorly soluble drug has been employed successfully. Seedhar N. *et al.*,^[9] studied solubility improvement of enrofloxacin using a series of co-solvents and surfactants with solubility increase up to 26 times. Commonly used non-ionic surfactants are lauroyl macroglycerides, castor oil, di-fatty acid ester of low molecular weight polyethylene glycol.

Salt formation

Dissolution rate of particular salt is usually different from that of parent compound. Sodium and potassium salt of weak acid dissolve more rapidly than that of pure salt. Limitation of salt formation includes epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation, patient compliance and commercialization.^[10]

pH adjustment

Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weakly acidic drugs increase the solubility of that drug, those excipients that act as alkalinizing agents may increase the solubility of weakly basic drugs.^[11]

Hydrotrophy

Hydrotrophy is a solubilization phenomenon in which solubility of poorly water soluble drug is enhanced to many folds by using sodium benzoate, urea, sodium citrate, and sodium salicylate.^[12]

Rasool A.A. *et al.*,^[13] improve solubility of many drugs, i.e., diazepam, griseofulvin, testosterone, progesterone, and 17-estradiol in presence of nicotinamide and related compounds.

All solubilities were found to increase in nonlinear fashion as a function of nicotinamide concentration.

Solid dispersion

Chiou and Riegelman 1971^[14] define solid dispersion as group of solid products consisting of at least two different components, generally, a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Solid dispersion can also be referred as the dispersion of one or more active ingredients in an inert matrix at solid state prepared by the melting, solvent, and melting solvent method.

Types of solid dispersion

On the basis of molecular arrangement, six types of molecular dispersion can be distinguished. They are described in Table 1.^[15]

Solid eutectic mixture

A simple eutectic mixture consists of two components which are completely miscible in liquid state but to a limited extent in solid state. These are prepared by rapid solidification of fused melt of two components. When a mixture of poor water soluble drug and water soluble carrier is dissolved in aqueous medium, the carrier is dissolved rapidly, releasing very fine crystal of drug.^[16]

Solid solution

In a solid solution, the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size responsible for increase in dissolution rate. On the extent of miscibility of two components, solid solution is classified as continuous and discontinuous. In continuous solid solution, the two components are miscible in the solid state in all proportions. In discontinuous solid solutions, the solubility of each of the components in the other component is limited.^[17]

Table 1: Types of solid dispersion

Type	Matrix*	Drug**	Remarks	No. of phases
Eutectics	C	C	The first type of solid dispersion prepared.	2
Amorphous precipitation in crystalline carrier	C	A	Rarely encountered.	2
Solid solution				
Continuous solid solution	C	M	Miscible at all composition, never prepared.	1
Discontinuous solution	C	M	Partially miscible, two phases even though drug is molecularly dispersed.	2
Substitutional solid solution	C	M	Molecular diameter of drug differs less than 15% from the matrix diameter. In that case the drug and matrix are substitutional.	1 or 2
Interstitial solid solution	C	M	Drug molecular diameter less than 59% of matrix diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2
Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix.	2
Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate. Many solid dispersion are of this type.	2
Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling, many complexes especially with PVP.	1

*A: Matrix in amorphous state, C: Matrix in crystalline state. **A: Drug dispersed as amorphous clusters in matrix, C: Drug dispersed as crystalline particles in the matrix, M: Drug molecularly dispersed throughout the matrix

Glass solution and suspension

A glass is a homogeneous glassy system in which solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. Characterization of the glassy state is transparency and brittleness below the glass transition temperature.^[18]

Amorphous precipitations in crystalline carrier

In the group of dispersions drug is precipitated out in amorphous form while in simple eutectic mixture it is in crystalline form. Example: Sulfathiazole in crystalline urea.^[19]

Mechanism responsible for solubility enhancement from solid dispersion

A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability.

Reduced particle size

When the solid dispersion is exposed to aqueous media, the carrier dissolve and the drug release as fine colloidal particles. The resulting enhanced surface area results in higher dissolution rate of poor water soluble drugs.^[14]

Drug in amorphous state

Poor water soluble crystalline drugs in amorphous state tend to have higher solubility.^[20] This is because no energy is required to break crystal lattice in amorphous state during dissolution.

Particles with high porosity

Particles in solid dispersion have been found to have high porosity.^[21] The increased porosity of solid dispersion particles hastens the drug release profile. Increase in porosity depends on carrier properties, i.e., linear polymers results in larger and more porous particles than that of reticular particles.

Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement has been verified in solid dispersion.^[22] Carrier with surface activity, i.e., cholic acid and bile salt can significantly increase the wettability property of drug results in enhanced dissolution profile.

Method of preparation of solid dispersion

Sekiguchi *et al.*, (1961) reported the formulation of eutectic mixture that leads to enhancement of solubility of water soluble drugs and thereby bioavailability. As Sulphathiazole – urea eutectic combination served as example for preparation of poor water soluble drug in highly water soluble carrier.

Hot melt method

Sekiguchi and Ovi^[23] used a hot melt method to prepare simple eutectic mixture that was the very first solid dispersion created for pharmaceutical application. In this preparation dispersion consisted of Sulphathiazole and urea as a matrix which were melted, followed by cooling step. Limitation of this method

includes miscibility of drug and carrier and thermo stability problems. An important advantage of this method is that the drug carrier mix subjected to elevated temperature for about one minute only, so that thermolabile drugs can be processed. Another alternate for thermolabile substances is by hot spin melting.^[24]

Solvent method

Tachibani and Nakumara^[25] were the first to dissolve both drug and carrier in a common solvent and then evaporate the solvent under vacuum that enabled them to produce a solid solution of highly lipophilic beta-carotene in PVP.

Evaporation method was taken by Mayersohn and Gibaldi.^[26] They prepared solid solution of Griseofulvin and PVP in chloroform with enhanced dissolution up to 11 times. Bates introduced the term co-precipitate to describe solid dispersion.

An important prerequisite for manufacturing the solid dispersion using solvent method is solubility of drug and carrier in solvent. Another issue is to remove solvent because of toxicity issue of organic solvent.

To dry the solution vacuum drying is always used. Solution is dried by the application of vacuum and moderate heating. Another drying technique is spray drying. Solution is dispersed in hot air as fine particles results in evaporation of solvent and solid dispersion is formed within seconds. An alternate to drying techniques is freeze drying. Advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of solid dispersion. Another advantage include the risk of phase separation is minimized. An even more promising drying technique is spray drying. The solvent is sprayed into liquid nitrogen and cold dry air and then frozen droplets are subsequently lyophilized.

Supercritical fluid process

This technology has been introduced in late 1980s and early 1990s. Since the first experience of Hannay *et al.*, in 1879^[27], a number of techniques has been developed and patented in the field of SCF process. SCF technique can be applied to the preparation of solvent-free solid dispersion dosage form to enhance the solubility of poorly soluble compounds. A solid dispersion of Carbamazepine in polyethylene glycol (PEG) 4000 increased the rate and extended the dissolution of Carbamazepine. In this method, a precipitation vessel was loaded with solution of Carbamazepine and PEG-4000 in acetone, which was expanded with supercritical CO₂ from the bottom of the vessel to obtain solvent-free particles.

SCFs either as solvent: Rapid expansion from supercritical solution (RESS) or as antisolvent: Gas antisolvent (GAS) and supercritical antisolvent (SAS).

In the supercritical fluid antisolvent technique carbon dioxide is used as antisolvent for the solute. The use of supercritical carbon dioxide has many advantages because of its low temperature

and pressure that makes it attractive for processing heat labile pharmaceuticals.

Other attractive features for use of carbon dioxide as supercritical fluid are non-toxicity, non-flammability, inexpensiveness. Removal of carbon dioxide from polymeric material is also easier, even through small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to consumer.^[28]

Melting solvent method

This method involves the unique advantages of both the solvent and fusion method. It involves the preparation of solid dispersion by dissolving the drug into suitable liquid solvent and then incorporating the solution directly into the melt of polymer (PEG). This is further evaporated until clear, solvent-free film. Film is further dried to a constant weight. From a practical standpoint, it is only limited to drugs with a low therapeutic dose, e.g., below 50 mg.^[29]

Spray drying

The manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920. This spray method was initiated by atomizing suspension or solution into fine droplet followed by a drying process, resulting in solid particles.

The operating condition and dryer design depends upon the product and require powder specification.^[30] Rankell *et al.*, prepared SD(s) of loperamide with PEG 6000 by this technique with enhanced dissolution.

Lyophilization method

Lyophilization has been thought of a molecular mixing technique in which drug and carrier are co-dissolved in common solvent, frozen, and sublimed to obtain a lyophilized molecular dispersion. Various scientists have successfully investigated the potential application of lyophilization in manufacturing SDs.^[31]

Electrostatic spinning method

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. In this process, electrostatic field involved over a conductive capillary attaching to a reservoir containing a polymeric solution and a conductive collective screen. Itraconazole/HPMC has been prepared using this technique.^[32]

Inclusion complexes

Inclusion complexes are formed by insertion of non polar molecule (known as guest) into the cavity of another molecule or group of molecule (known as host). The most commonly used host molecules are cyclodextrins. Cyclodextrin are cyclic oligomers produced by enzymatic degradation of starch by cyclodextrin glucosyl transferase (CGT). Naturally occurring cyclodextrin are α cyclodextrin, β cyclodextrin, and γ cyclodextrin.^[33] The improvement of solubilization ability within water soluble polymer/drug-included CD aggregates require less cyclodextrin

to solubilize the same amount of drug. Solid inclusion complexes are prepared by various methods such as kneading method co-precipitation, neutralization, co-grinding, spray drying method, and microwave irradiation method.

Evaluation parameter of solid dispersion

Phase solubility study

For this study excess amount of drug is added to aqueous solution of carrier in specific dissolution media containing increasing concentration of carrier. Then flask is sealed and shaken at 37°C in thermostatically controlled water bath. Then sample is filtered, filtrate is suitably diluted, and analyzed spectrophotometrically at suitable wavelength.^[34]

Drug content

In this defined amount of solid dispersion is dissolved in suitable solvent then after appropriate dilution concentration is measured by UV spectrophotometry. HPLC is also an useful tool for drug content measurement. Calibration graph is constructed by peak area verses concentration of drug.^[35]

Powder X-ray diffraction studies

Powder X-ray diffraction (PXRD) can be obtained by employing X-ray diffractometer. It is a method of determination of arrangement of atom within the crystal, in which a beam of X-ray strikes a crystal and diffracts into various specific directions. From the angles and intensities of these diffracted beams, X-ray diffractometer can produce a three dimensional picture of the densities of the electrons within the crystal. From this electron density, the mean position of atoms in the crystal can be determined, as well as their chemical bonds and various other information.^[36]

Dissolution studies

Dissolution study of given solid dispersion can be performed according to USP paddle (100 rpm) in distilled water 0.1N HCl equilibrated at 37±0.2°C. Five-milliliter samples were taken and immediately replaced with fresh dissolution medium at 5, 10, 15, 30, 45, 60, and 120 min. Then, aliquots are filtered through 0.45- μ m membrane syringe filter. Amount of drug release is measured by UV spectrophotometrically at suitable wavelength.^[37]

Interaction studies

Thermal data analyses

In differential thermal analysis, the temperature difference that develops between a sample and an inert reference material is measured, when both are subjected to identical heat under nitrogen atmosphere on an aluminium pan at the rate of 10°C/min. The related technique of differential scanning calorimetry relies in differences in energy required to maintain the sample and reference at an identical temperature. Thermal data analysis of the DSC thermograms is obtained.^[38]

Fourier transform infrared spectroscopy

FTIR can be employed to characterize the possible interaction between the drug and the carrier in solid state by conventional

KBr method. In this method about 10 mg of sample is mixed with dried KBr of equal weight and sample is scanned over a frequency range 4000-500 cm^{-1} and FTIR spectra of the sample are obtained using FTIR spectrophotometer.

Stability study

The stability of the solid dispersion preparation should be carried out at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH and then sample is evaluated for saturated solubility, *in vitro* release and change in crystallinity using DSC and XRPD.^[35]

Microscopy

Optical microscopy method and scanning electron microscopy can be utilized for particle size analyses. Electron microscopy utilizes electron transmission for ascertaining particle size and morphology.^[35]

CONCLUSION

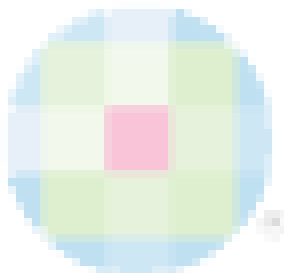
This article concludes that solubility of poorly water-soluble drugs is an important concept to reach into systemic circulation to show its pharmacological response. Dissolution is a rate limiting step for drug absorption of poorly water-soluble drugs. Experience with solid dispersion over the last 20-30 years indicates that this is a fruitful approach to increase the solubility of poorly water-soluble drugs. Increasing number of poorly water-soluble drug candidates as well as improvements in solid dispersion manufacturing methods strongly favour the role of solid dispersion in solubility enhancement of poorly water-soluble drugs.

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